REMARKS/ARGUMENTS

Claims 1, 11-13, 15, 17-23, 26, 27, 30 and 31 are active.

Applicants sincerely thank Examiners Basi and Pak for the courtesy of discussing this case with them and their legal representatives. During this discussion, the ejection of the claims on the grounds of lack of utility and enablement were discussed. In particular, it was explained that

(A) the evidence provided in the specification in light of what was known in the field at or before the time the application was filed supports a substantial and credible utility for the claimed subject matter

(B) the evidence relied upon in the Action to maintain, in particular, the utility rejection under § 101 was misapplied.

I. Utility and Enablement is established by the screening methods described in the application

Utility is also present in the application as it relates to, for example, generating antibodies to investigate the presence of ionic channels in various tissues (see page 6 of the application) as well as the other screening methods (see pages 8-10 of the application;) that allow for the investigation of and identification of compounds which have modulating effects on the function of the protein channel. Indeed, these later screening embodiments are captured at least in part in pending claim 22.

II. Utility is present because the application provides a real nexus between the claimed channels and pathological conditions

The specification specifically discloses that the connection between ASIC channels and ischemic pain and neurodegeneration is through the induction of channel activity and the resulting ion influx.

A role in the pain and neurodegeneration pathways imparts both a specific and substantial utility to the claimed channel; for example, for use as a drug screen for therapeutic compounds active against these particular diseases. The Applicants have also presented supporting data in the specification, discussed relevant knowledge in the prior art, and have identified post-filing publications that describe and confirm the relationship between ASIC channels and disease states. The Applicants assert that this evidence of record is probative of the asserted utility and therefore supports the credibility of the asserted utility.

The Applicants have demonstrated that the ASIC channels are expressed in the brain and do exhibit activity at pH 6.5 (See Figs. 7 and 5b of Applicant's specification). Furthermore, Ca^{2+} influx is known to play a role in neurodegeneration, and the Applicants' data shows that the claimed channel is Ca^{2+} permeable (See Applicant's specification Fig. 5e and Choi. 1995. Trends Neurosci. 18 (2): 58-60). The C. *elegans* model of neurodegeneration shows that hyperactivity of several homologs of the claimed channel results in cell death and, thereby, further supports the asserted relationship (See Driscoll *et al.* 1991. Nature. 349: 588-593, Chalfie *et al.* 1993. Nature. 361 (6412): 504, Chalfie *et al.* 1990. Nature. 345 (6274): 410-416, See also page 2, line 27 of the Applicants' specification). It was also known at the time of filing, that ASIC2a (MDEG) hyperactivity leads to cell death in mammals (See Waldmann *et al.* 1996. J Biol Chem. 271 (18): 10433-10436). The demonstrated relationship between brain acidosis, channel hyperactivity, calcium influx, and cell death is the nexus that connects the channels to neurodegeneration. While the function of ASIC channels in healthy brains is not precisely known, this does not diminish the fact that the protein can have an established role in disease. For example, the role of prion proteins or beta amyloid proteins in healthy brains is unknown but it is commonly agreed that each have a well-established link to diseases such as Jakob-Creutzfeld (prions) or Alzheimer's (beta-

amyloid). See also, the attached publication by Wong et al suggesting a link between ASIC channel activity and Huntington's disease.

The neuronal ASIC channels described in the specification have properties that are different from their homologues, the epithelial sodium channel subunits (See ENaChs, See Rossier *et al.* 2002. Annu Rev Physiol. 64: 877-897). Indeed, the ASIC channels and the C. elegans degenerins are a distinct branch in the phylogenetic tree that is separate from the epithelial sodium channel subunits. (See Applicants' Specification, Figure 3). Furthermore, the epithelial sodium channels are blocked by amiloride concentrations that are about two orders of magnitude lower than those required to block ASIC channels (Applicants specification, pg. 18, ln. 23; Figure 6 d, e). Epithelial amiloride sensitive sodium channels, unlike ASICs, are constitutively active, are not activated by extracellular acid, and are not expressed in neurons. Thus, both biophysical properties and pharmacology allow classification of the different members of this ion channel family.

The specification establishes that ASIC mRNA is expressed in small pain sensing neurons of the dorsal root ganglion (Applicants' specification, pg. 19, ln. 19, Figure 8). Furthermore, contact of the claimed channels with acid induces an inflowing current with similar electrophysiological properties (inactivation kinetics, acid sensitivity, ionic selectivity, single channel conductance) to proton activated cationic channels of sensory neurons (Applicants' specification, pg. 17, ln. 24 ff, Figures 5 and 6)

The specification further shows that amiloride inhibits the inflowing current though ASIC channels caused by protons (Applicants specification, pg. 18, ln. 23; Figure 6 d, e). The pharmacological properties of a cloned ion channel are commonly used in combination with the biophysical properties to verify that the identity of a cloned channel is the same as the native ion channel. Thus, the fact that both the ASIC channels and the native acid-

activated cation channels in sensory neurons are blocked by amiloride strongly suggests that ASIC channels are the acid sensors in sensory neurons.

The Applicants assert that arguments presented above sufficiently verifies a credible, substantial, specific utility. Further. as support of the credibility of the asserted utility, the Applicants point to the over 300 journal articles that cite the underlying research of the present application (See Waldmann *et al.* 1997. Nature. 386 (6621): 173-177). These articles, especially the number that focus on neurodegeneration and pain, are a convincing indication that those skilled in the art have indeed accepted that the claimed channels are directly connected to the asserted disease states. Furthermore, the magnitude of citations demonstrates that the research underlying the present application was not only accepted by those skilled in the art, but also provided guidance for further research. If, as the Office Action alleges, the Applicant's data was not probative or convincing of a role in pain or neurodegeneration, other scientists would not have pursued further research into the role of ASICs in pain and neurodegeneration. As the specification and the frequently cited research contains the exact same data and conclusions regarding the role of ASICs in disease pathways, many individuals skilled in the art have indeed understood and accepted the asserted utility.

Consequently, one skilled in the art would consider the asserted utility to be credible, and therefore withdrawal of the rejections is requested.

A Notice of Allowance is also requested.

Respectfully submitted,

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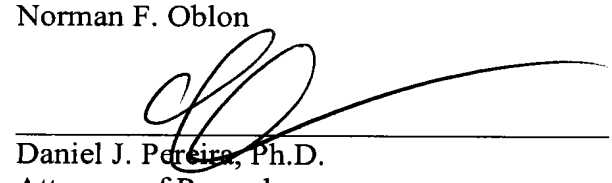

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